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10/542,940	04/10/2006	Emma Terricabras Belart	09605.0012	9204

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EXAMINER	
MOORE, SUSANNA	

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,940	TERRICABRAS BELART ET AL.	
	Examiner	Art Unit	
	SUSANNA MOORE	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14 and 19-22* is/are pending in the application.

4a) Of the above claim(s) *20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7,12,14 and 19* is/are rejected.

7)☒ Claim(s) *5 and 8-11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/4/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments, see Remarks, filed 3/4/2009, with respect to Nonfinal Office Action mailed 12/5/2008 have been fully considered. Thus, this is a Final Office Action since no new rejections are being made. In summary, claims 1-12, 14 and 19-22 are currently pending. Claims 20-22 are currently withdrawn. Thus, claims 1-12, 14 and 19 are currently under consideration.

Claim Objections

The objection of claim 4 because of the proviso is **withdrawn** based on the amendments.

Claims 5 and 8-10 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 20-22 are objected to because of the following informalities: this application contains claims 20-22, drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01. Appropriate correction is required. Applicant traverses the above objection for the "reasons of record." Applicant is reminded of the following section of the M.P.E.P.:

37 CFR 1.475. Unity of invention before the International Searching Authority, the International Preliminary Examining Authority and during the national stage.

A. Combinations of Different Categories of Claims

The method for determining unity of invention under PCT Rule 13 shall be construed as permitting, in particular, the inclusion of any one of the following combinations of claims of different categories in the same international application:

(A) In addition to an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and an independent claim for a use of the said product; or

(B) In addition to an independent claim for a given process, an independent claim for an apparatus or means specifically designed for carrying out the said process; or

(C) In addition to an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product and an independent claim for an apparatus or means specifically designed for carrying out the said process.

A national stage Application is entitled to a product, a process and a method of intended use as independent claims, not a plurality of each category. Claims 20 and 22 are drawn to product claims, like claim 1, which is drawn to a product claim. Claim 21 is drawn to a method of intended use, like claim 19, which is drawn to a methods of intended use. Thus, the objection is **maintained**.

Claim 4 is objected to because of the following informalities: the formula at the bottom of page 6 is too close to the page number. Please move the formula. Appropriate correction is required.

Claim 11 is objected to because of the following informalities: a comma should be placed after each species listed in said claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6, 7, 12, 14 and 19 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 1 and 4 the "alkylene groups" defined as a variable on R_3 is unduly functional. R_3 is defined as an aryl or heteroaryl and alkylene is CH_2, which is divalent. Thus, claims 1-4, 6, 7, 12, 14 and 19 are vague.

Applicant traverses the above rejection by stating, "The variable G, within the definition of R_3, can be a "monocyclic or bicyclic aryl or heteroaryl group comprising from zero to four heteroatoms which group is optionally substituted by one or more substituents .... " See e.g., claim 1. Thus, R_3 is not defined in the claims as "an aryl or heteroaryl," although the variable G, within the context of R_3, may be chosen from an aryl and heteroaryl." This is not found persuasive. Applicant is correct that the variable R3 is defined as "$(CH_2)_n$-G" and G is an aryl or heteroaryl. The rejection is for the subsection (ii) where G is substituted with an "alkylene

group." Said alkylene group is not part of the $(CH_2)_n$ linker connecting to the thieno[2,3-d]pyrimidine core. Said alkylene group is a substituent on G, even when n=0. Thus, the rejection is **maintained**.

The rejection of claim 2 for reciting the limitation "a cycloalkyl group" is **withdrawn**.

The rejection of claim 2 for reciting the limitation "a hydroxyl group" is **withdrawn** based on the amendments.

Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The insertion of "or a pharmaceutically acceptable salt thereof" into claim 2 is new matter. Applicant should point specifically in the Specification to where there is support for said genus with added limitation to overcome the rejection.

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which

it is most nearly connected, to make and/or use the invention. Such a utility cannot be deemed enabled. .

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(A) Breadth of claims.

(a) Scope of the compounds. Owing to the range of 4 primary variables, millions of thieno[2,3-d]pyrimidine compounds are embraced.

(b) Scope of the diseases covered. Claim 19 is drawn to asthma, atopic dermatitis, chronic obstructive pulmonary disease, Crohn's disease, type I and type II diabetes, lymphoid leukemia, multiple sclerosis, alograft rejection after organ transplantation, psoriasis, rheumathoid arthritis, and ulcerative colitis. Several of the umbrella terms above will are discussed in more detail below.

Chronic Obstructive Pulmonary Disease (COPD) is a slowly progressive disease of the airways that is characterized by a gradual loss of lung function. COPD includes chronic obstructive Bronchitis (which involves inflammation and eventual scarring of the bronchi) and

emphysema (enlargement and destruction of the alveoli). Emphysema comes in several forms, including Congenital Lobar Emphysema, Bullous Emphysema, Centrilobular Emphysema (Proximal acinar emphysema), Panacinar (panlobular), Distal acinar (paraseptal) as well as Alpha-1 antitrypsin (AAT) deficiency, which is the genetic form of emphysema; patients often have both a form of bronchitis and emphysema. Ordinary chronic bronchitis is sometimes included with COPD even if there is no actual obstruction, and asthmatic bronchitis is generally included in COPD as well.

There are two forms of diabetes, type I and type II. Type I, formerly known childhood diabetes, is characterized by loss of the insulin-producing beta cells of the islets of Langerhans of the pancreas leading to a deficiency of insulin. Type II, previously known as adult-onset diabetes, is due to a combination of defective insulin secretion and defective responsiveness to insulin (often termed insulin resistance or reduced insulin sensitivity), almost certainly involving the insulin receptor in cell membranes.

(B) The nature of the invention and predictability in the art: The invention is directed towards medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(C) Direction or Guidance: That provided is very limited. The dosage range information 10-600 mg/day is generic, the same for the many disorders covered by the specification. Thus, there

is no specific direction or guidance regarding a regimen or dosage effective specifically for the treatment of the vast number of diseases covered by the scope.

(D) State of the Prior Art: These compounds are highly substituted thieno[2,3-d]pyrimdines. So far as the examiner is aware, no highly substituted thieno[2,3-d]pyrimdines of any kind have been used for the treatment of the diseases covered by the scope as outlined above.

(E) Working Examples: There are 135 working examples of compounds on pages 31-101. The instant compounds were examined in an assay measuring in vitro binding to PDE7. The results are summarized on page 28 of the Specification. There are no in vivo working examples for the treatment of any diseases embraced by the Scope of diseases above.

(F) Skill of those in the art: These diseases and disorders covered by the Scope of diseases above cannot be treated generally by any one drug. These are all different diseases and disorders, which occur at different locations and by different modes of action in the body.

The prior art knows that there never has been a compound capable of treating cancer generally. "The cancer therapy art remains highly unpredictable, and no example exists for efficacy of a single product against tumors generally." (<http://www.uspto.gov/web/offices/pac/dapp/1pccba.htm#7 <http://www.uspto.gov/web/offices/pac/dapp/1pccba.htm>> ENABLEMENT DECISION TREE, Example F, situation 1) There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer

generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology.

Regional enteritis (Crohn's disease or ileitis) is an autoimmune disorder, which is associated with the presence of Mycobacterium paratuberculosis. It can affect any part of the gastrointestinal tract but most commonly affects the ileum. The inflammation is controlled primarily by regulation of diet, antibiotics if abscesses and fistulas are present, sometimes Prednisone and other corticosteroids, and surgery.

Persons with COPD typically develop smaller air passageways, which can become clogged with mucus and have partially destroyed alveoli. There is no pharmaceutical treatment for COPD per se. Instead, treatment is supportive and designed to relieve symptoms and improve quality of life. Thus, oxygen is often given to partially compensate for the loss of lung function. Bronchodilators can expand passageways in the lungs, Corticosteroids can reduce inflammation and Antibiotics can ward off bacterial infections, but none of these treat the COPD itself.

Crohn's disease, rheumatoid arthritis, psoriasis and ulcerative colitis are all autoimmune diseases which are treated differently. Rheumatoid arthritis is treated with an alpha-TNF inhibitor, e.g. Enbrel. Currently there is no actual treatment for multiple sclerosis itself, only management of symptoms. Psoriasis is a hyperproliferative skin disease of the immune system, which is hard to treat.

(G) The quantity of experimentation needed: Owing especially to factors A, C, E and F, the amount of experimentation is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Applicant traverses the above rejection by stating several points which will be discussed below.

Applicant states, "Applicants have presented evidence that the compounds of the invention are effective PDE7 inhibitors. See, e.g., specification at p. 28-29." This is correct. However, there is no correlation between the inhibition of PDE7 and the treatment of those disease listed in claim 19.

Applicant goes on to recite, "However, it is well established that the type of *in vitro* studies described in the specification may be sufficient to satisfy §112, even in the absence of *in vivo* studies. For example, the M.P.E.P. cites *In re Brana* (51 F.3d 1560 (Fed. Cir. 1995)) as an example where the Federal Circuit ruled that *in vitro* data did support *in vivo* applications. M.P.E.P. §2164.02, under Correlation: *In Vitro/In Vivo*." This is also correct. However, in Brana 5-nitrobenzo[de]isoquinoline-1,3-dione compounds were disclosed as compounds with "a better action and a better action spectrum as antitumor substances" than known benzo [de]isoquinolines, namely those in the Paull reference, et al., *Computer Assisted Structure-Activity Correlations, Drug Research, 34(II),* 1243-46 (1984) (Paull). Paull describes a computer-assisted evaluation of benzo [de]isoquinoline-1,3-diones and related compounds which

have been screened for antitumor activity by testing their efficacy *in vivo* against two specific implanted murine (i.e., utilizing mice as test subjects) lymphocytic leukemias, P388 and L1210. These two *in vivo* tests are widely used by the National Cancer Institute (NCI) to measure the antitumor properties of a compound. Thus, a strong *in vitro* to *in vivo* assay correlation was defined in the reference for lymphocytic leukemias. This is not case in the instant Application.

Applicant goes on to state, "These statements by the Examiner, however, ignore an explicit limitation in the claims explaining that to the type of pathological conditions or diseases that can be treated herein are those "susceptible to amelioration by inhibition of PDE7," which is a property shown by the compounds of the invention." The Examiner has not ignored any limitations in the claims. As mentioned previously, there is not a correlation between the inhibition of the PDE7 enzyme and the diseases in claim 19.

Applicant has submitted several references which will not be addressed.

The reference by A. Nakata et al., *Clinical and Experimental Immunology*, 128:460-466 (2002), states, "However, the role of PDE7 in T cell function is still unclear, as a selective PDE7 inhibitor had not been established." See page 460, right-hand column, the last line in the first paragraph. The reference clearly states the role of PDE7 was not well understood. Furthermore, the reference states, "PDE7 may play a critical role in the regulation of human T cell function, and thereby selective PDE7 inhibitors have the potential to be used to treat immunological and inflammatory disorders." See the last line in the abstract. The reference concludes with "In conclusion, PDE7 has the potential to regulate human T cell functions including cytokine production, proliferation and expression of activation markers. This suggests the possible management of various immunological diseases by treatment with selective PDE7 inhibitors."

See page 465, bridging paragraph. The term "may" is suggestive of a possibility. It doesn't imply enablement. As was stated in *Exparte Bhide*, 42 USPQ2d 1441 (1/31/1996), "one skilled in the art would understand the "may be useful" and "may also act as inhibitors" statements to be possibilities -- not actual statements of use." Therefore, this reference does not provide firm evidence that PDE7 inhibitors are effective in treating the disease outlined above under Scope.

Smith, S. et al. AJP Lung Cell Molecular Physiology 284:279-289 (2003) recites, "In conclusion, … As PDE7A inhibitors become available, it is certain that a major research effort will begin to determine the functional role of PDE7A in these cells and whether such compounds have anti-inflammatory activity similar to rolipram without the associated gastrointestinal, cardiovascular, and central nervous system side effects." See page L287, last paragraph. Furthermore, the abstract states, last line, "As the expression of PDE7A mirrors the distribution of PDE4 we speculate that this enzyme could be a target for novel anti-inflammatory drugs." The role of PDE7 was still unknown and the role speculative.

Martinez A. et al. *Journal of Medical Chemistry,* 2000, 43(4): 683-689, Martinez discusses studies regarding specific PDE7 inhibitors that can be used for the treatment for T-cell dependent disorders, stating, "Recently a functional role of PDE7 in T-cell activation has been described, for the first time; therefore, selective inhibitors of PDE7could be a new strategy to treat T-cell-related diseases. On the other hand, the identification of selective inhibitors of the PDE7 isoenzyme could help to understand the functional role of this cAMP-specific PDE." Here again, the reference does not provide a definitive set of diseases which can be treated by the inhibition of PDE7.

Applicant has also provided several citations to US patents, US 7122565, 6753340, 6884800, and 6531498. This is true, however, each Application must be enabled and is taken on its own merits.

Thus, the rejection is **maintained**.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUSANNA MOORE whose telephone number is (571)272-9046. The examiner can normally be reached on M-F 8:00-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Susanna Moore/
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